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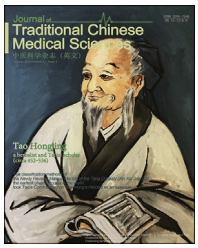

Effects of *Zingiber officinalis* (WILLD.) ROSC. Membranes on minor recurrent aphthous stomatitis: a randomized pragmatic trial

Qian Du [a], Shenglou Ni [a], Lin Guo [a], Wenjie Song [a], Kun Zhao [a], Ni Liu [a], Xinrong Wang [a], Xun Ma [a], Yanling Fu [a,*], Quanming Tan [b]

[a] *Beijing University of Chinese Medicine, Beijing 100029, China*
[b] *Singapore Thong Chai Medical Institution, Thong Chai Building 169874, Singapore*

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KEYWORDS
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Abstract *Objective:* To evaluate the effects of dried ginger rhizome (DGR; *Zingiber officinalis* (WILLD.) ROSC.), prepared as a membrane, in minor recurrent aphthous stomatitis (miRAS) treatment and explore its mechanism of action by detecting changes in levels of epidermal growth factor (EGF) and tumor necrosis factor (TNF)-α in saliva.
Methods: Fifty-nine miRAS patients were enrolled in this study. The number of participants in the dried ginger rhizome membrane (DGRM) group was 30, and 29 were in the placebo membrane (PM) group. Sixty sealed envelopes containing either type of membrane were coded randomly. Investigators and participants were blinded to group assignments. A visual analog scale (VAS) was used for pain, follow-up information for healing time, and enzyme-linked immunosorbent assays to measure the concentrations of EGF and TNF-α.
Results: In terms of VAS, there was a significant difference between pre- and post-DGRM treatment ($P < .001$), but not so for the PM group ($P > .05$). A significant difference was observed in the healing time between the two groups (6.08 (2.712) *vs*. 8.04 (2.142) days). The mean healing time in the DGRM group was shorter than that in the PM group ($P < .05$). In both groups, the salivary EGF concentration decreased significantly after treatment ($P < .05$), but the mean level in the DGRM group was significantly lower than that in the PM group ($P < .05$). The mean TNF-α level in both groups was increased significantly after treatment ($P < .05$), but patients who used DGRMs had a significantly lower level than that in the PM group ($P < .05$).

* Corresponding author.
E-mail address: fuyanling@bucm.edu.cn (Y. Fu).
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Conclusion: The present study provides evidence that DGRMs are effective treatment for RAS. Dried ginger rhizome has obvious effects on pain relief, shortening of healing time, reducing the EGF level in saliva, and has an inhibitory effect on TNF-α release.

Introduction

Recurrent aphthous stomatitis (RAS) is a relatively common disease affecting the oral mucosa. According to epidemiologic data, 2%—66% of the worldwide population is affected by RAS.[1–2] It is characterized by painful, recurrent ulcerations of the oral mucosa and can be classified clinically into three categories based on the diameter of mouth ulcers: minor (<1 cm), major (>1 cm), and herpetiform. Minor recurrent aphthous stomatitis (miRAS) is the most common manifestation, and occurs in 75%—80% of patients. Ulcers due to miRAS are <1 cm in diameter (usually 2—5 mm) and heal spontaneously in 7—14 days. Although common, RAS has an unpredictable disease course.[3–4]

The exact pathogenesis of RAS is not known,[5–9] but inflammation plays an important part in it. Considerable evidence suggests that focal immune dysfunction exerts a significant influence. Thus, anti-inflammatory and immunosuppressant drugs have been administered widely to miRAS patients. However, efficacious therapies that can prevent repeated bouts of ulceration are lacking. Mainstream treatments aim at alleviating pain, reducing functional disability, and facilitating healing.[10,11] Traditional Chinese medicine (TCM) could be used to treat RAS.

Dried ginger rhizome (DGR; *Zingiber officinalis* (WILLD.) ROSC.) is a common dietary adjunct contributing to the taste and flavor of foods, and is also an important Chinese herb. Dried ginger rhizome is a frequently used ingredient in TCM-based treatment of RAS.[12]

Some studies have shown that DGR has anti-inflammatory, antioxidant, analgesic and antiseptic effects.[13—15] Yang et al reported that DGR is a transient receptor potential cation channel subfamily V member 1 (TRPV1) agonist. Initially, DGR can sensitize sensory endings within inflamed tissue and produce a "warm" feeling, then desensitize the tissue and relieve pain.[16,17] Some researchers have shown that water extracts of DGR have good effects against pain caused by different stimuli, and can reduce the pain caused by inflammation.[18] Luo et al used a component of DGR, 6-gingerol,[19] to treat oral stomatitis in mice, and showed a shortened healing time and improvement of the cure rate.[20]

We evaluated the effects of a water extract of DGR, in the form of an oral membrane, on miRAS.

Methods

Ethical approval

This was a double-blind, placebo-controlled clinical pragmatic trial undertaken at the Beijing University of Chinese Medicine (BUCM; Beijing, China). The study was approved by the Ethics Committee of BUCM (2017BZHYLL0308). All participants were informed of the purpose, general contents, and data use of our study. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR-OPR-17013127).

Patient selection

This was an exploratory study so the patient cohort was small. Participants were selected from the general population of Beijing using flyers posted at various locations as well as e-mails to universities. People were enrolled after a diagnosis had been made by Professor Yanling Fu in the Guo Yi Tang Outpatient Department of BUCM in 2017.

Inclusion criteria were: (i) age > 18 years; (ii) a clear history of RAS occurring no less than four times a year; (iii) presentation with one or two ulcers measuring ≤ 10 mm in diameter for ≤ 48 hours and yet to receive treatment; (iv) ulcers that took > 5 days to resolve without treatment.

Individuals were excluded if they: (i) had underlying systemic disease(s) or a history of immunologic disorder(s); (ii) were taking immunomodulatory agents or systemic nonsteroidal anti-inflammatory drugs < 1 month before study commencement;[4] (iii) were smokers; (iv) were pregnant; (v) were (or had a history of) abusing drugs or alcohol; (vi) could not provide written informed consent.

Preparation membranes

Dried ginger rhizome (DGR; *Z. officinalis* (WILLD.) ROSC.) was purchased from a Tong Ren Tang outlet in Beijing. Using a ratio of DGR: water of 1:10, medicinal components were extracted by boiling in water for 6 hours. Then, extracts were filtered, concentrated, dried, ground and stored.

The resulting powder was mixed with polyvinyl alcohol $(PVA)_{1788}$ and prepared into a dried ginger rhizome membrane (DGRM). A placebo membrane (PM) containing the resulting powder at one-tenth the concentration of DGR and PVA_{1788} was prepared after we failed to create a DGRM at one-twentieth concentration of DGR.[21,22] There were no other ingredients in either type of membrane.

In dry storage, both types of membrane are non-adherent and can be applied readily as required. Upon contact with saliva at a lesion site, a sticky hydrogel is formed which adheres to the mucosa.

The prepared membranes were cut into squares of size 1.5 cm, and sealed in small plastic bags. The latter were encoded by a research pharmacist (Lin Guo) so that investigators and patients were both blinded to the type of membrane contained within.